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Unnatural Natural Products from the Transannular Cyclization of Lathyrane Diterpenes

Giovanni Appendino,*,† Gian Cesare Tron,† Tomas Jarevång,‡ and Olov Sterner*,‡,§

Università del Piemonte Orientale, DiSCAFF, Viale Ferrucci 33, 28100 Novara, Italy, and Department of Organic Chemistry, Lund University, P.O. Box 124, 22100 Lund, Sweden

appendin@pharm.unito.it

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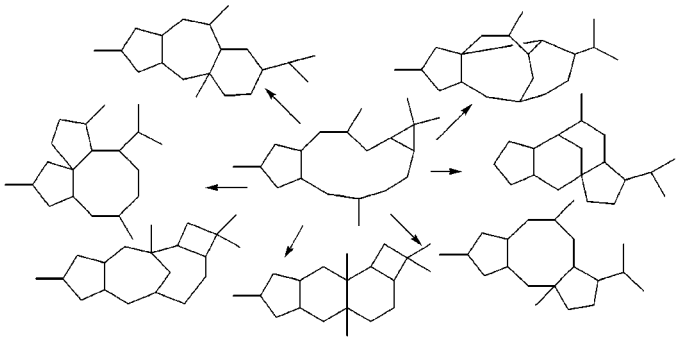
ABSTRACT



The potential of macrocyclic diterpenoids to afford natural product-like polycyclic compounds was demonstrated by the conversion of two lathyrane *Euphorbia* factors into a series of densely functionalized diterpenoids of unnatural skeletal type. Apparently, Nature is far from having fully exploited the built-in reactivity of these compounds to generate chemical diversity.

Natural products are a relatively small share of the known organic compounds (<1%) but have played a preeminent role in biomedical research for their ability to alter the function of proteins relevant to biochemical processes.[1] Natural products can only be obtained by fractionation of extracts, a slow and inefficient technology by modern standards of pharmaceutical research. To overcome this limitation, there has been an intense activity aimed at the expansion of the natural products pool through the generation of compounds mimicking their features. To address this issue, combinatorial synthesis using key fragments of natural products as core structures[2] as well as combinatorial biosynthesis[3] have been attempted. We describe a conceptually simple alternative which capitalizes on the potential chemical diversity encoded in natural polyolefins and their monoepoxides.

The propensity of medium-sized compounds to undergo transannular cyclization has been deftly harnessed by Nature to build thousands of polycyclic sesquiterpenoids and diterpenoids from various classes of medium-sized and macrocyclic precursors. Interest in this chemistry has mainly focused on the development of chemical mimics of alleged biogenetic relationships, and this has been highly successful

† Università del Piemonte Orientale.
‡ Lund University.
§ E-mail: olov.sterner@orgk2.lth.se.

(1) (a) Henkel, T.; Brunne, R. M.; Müller, H.; Reichel, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 643−647. (b) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969.

(2) For a review, see: Watson, C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1903. For a recent example, see: Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q. *Angew. Chem., Int. Ed.* **2000**, *39*, 734−739.

(3) For a review, see: Hertweck, C. *ChemBioChem* **2000**, *1*, 103−106.

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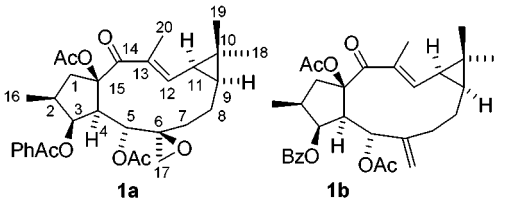
in the realm of sesquiterpenes.[4] Conversely, only unnatural isoprenoid skeletons have generally been obtained from the cyclization of medium-sized diterpenes,[5] suggesting that Nature is far from having fully exploited the potential of these compounds to generate chemical diversity.

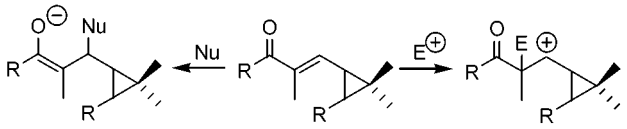
The possibility of tailoring the reactivity of macrocyclic diterpenes to go beyond natural products and the duplication of Nature has so far been largely overlooked. This is somewhat surprising, since diterpenoids are one of the most diverse classes of natural products in terms of cellular targets and are therefore of special value in programs of drug discovery. We have found that certain lathyrane diterpenoids are superb substrates for the generation of diversity, showing a reactivity that can be modulated over a vast range by the choice of a suitable acid, base, or radical trigger. This Letter reports the results obtained with acidic reagents in polar solvents.

The *Euphorbia* factors L_1 (**1a,** PhAc = $PhCH_2CO$)[6] and L_3 (**1b**) are easily available in multigram amounts from the seeds of the caper spurge (*Euphorbia lathyris* L.), an agricultural commodity.[7] Despite their origin, they are nonirritant and totally devoid of tumor-promoting activity.[8] On the other hand, interesting biological activities, including NGF mimicry[9] and inhibition of PgP,[10] a pump involved in the resistance to many anticancer drugs, have been documented for macrocyclic *Euphorbia* diterpenoids.



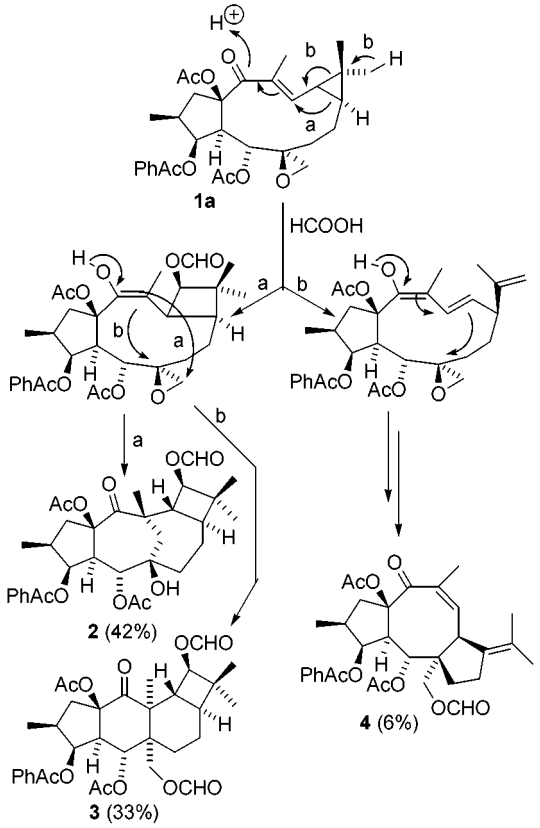
A preliminary investigation on the transannular cyclization of **1a** disclosed only the formation of compounds of unnatural skeletal type.[6,11] Their good isolation yield and structural complexity prompted us to further investigate the potential of **1a** and **1b** to generate chemical diversity. The captodative endocyclic double bond of these compounds was perceived as an important element for diversity-oriented synthesis, translating into the possibility of accommodating both a negative and a positive charge via formation of an enolate or an α-cyclopropyl cation, respectively (Scheme 1).

Scheme 1



In the event, treatment of **1a** with formic acid afforded a mixture of three compounds. The cyclobutanes **2** and **3** had already been described,[6,11] but their configuration should be revised as indicated in Scheme 2. The cyclooctanoid **4**

Scheme 2



derives from the vinylogous version of the transannular cyclization leading to **2** and **3** and showed isopropylene to isopropylidene isomerization. Interestingly, the product of *endo*-opening of the epoxide was not apparently formed in the vinylogous transannular cyclization.

Surprisingly, the 6(17)-deoxy analogue **1b** gave entirely different cyclization products (**5**, **6**), with changes in carbon−carbon connectivity limited to the γ-cyclopropyl enone moiety and an overall process somewhat reminiscent of a Nazarov reaction (Scheme 3). Thus, the dienol obtained by opening of the cyclopropane ring reacts in a vinylogous

(4) Appendino, G.; Jakupovic, J.; Cravotto, G.; Biavatti-Weber, M. *Tetrahedron* **1997**, *53*, 4681−4692. For a general review on the biosynthesis of sesquiterpenes, see: Cane, D. E. *Chem. Rev.* **1990**, *90*, 1089−1103.

(5) For a remarkable example, see: Nishizawa, M.; Imagawa, H.; Hyodo, I.; Takeji, M.; Morikuni, E.; Asoh, K.; Yamada, H. *Tetrahedron Lett.* **1998**, *39*, 389−392.

(6) Adolf, W.; Hecker, E.; Balmain, A.; Lhomme, M. F.; Nakatani, Y.; Ourisson, G.; Ponsinet, G.; Pryce, R. J.; Santhanakrishnan, T. S.; Matyukhina, G.; Saltikova, I. A. *Tetrahedron Lett.* **1970**, 2241−2244. Revised structure: Appendino, G.; Cravotto, G.; Jarevang, T.; Sterner, O. *Eur. J. Org. Chem.* **2000**, 2933−2938.

(7) Appendino, G.; Tron, G. C.; Cravotto, G.; Palmisano, G.; Jakupovic, J. *J. Nat. Prod.* **1999**, *62*, 76−79.

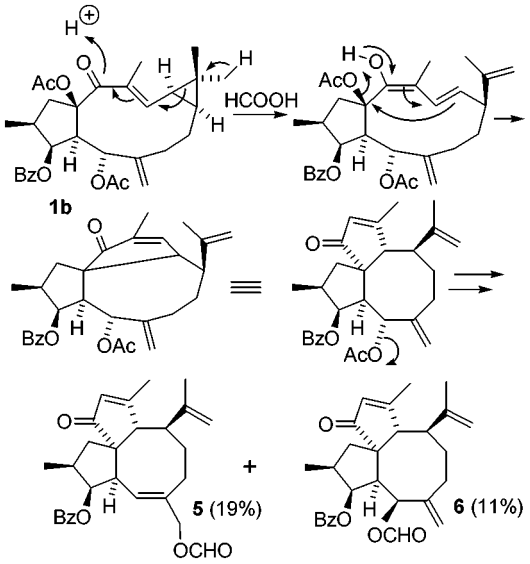
(8) Adolf, W.; Hecker, E. *Z. Krebsforsch.* **1975**, *84*, 325−344.

(9) Yamaguchi, K.; Uemura, D.; Tsuji, T.; Kondo, K. *Biosci. Biotech. Biochem.* **1994**, *58*, 1749−1754.

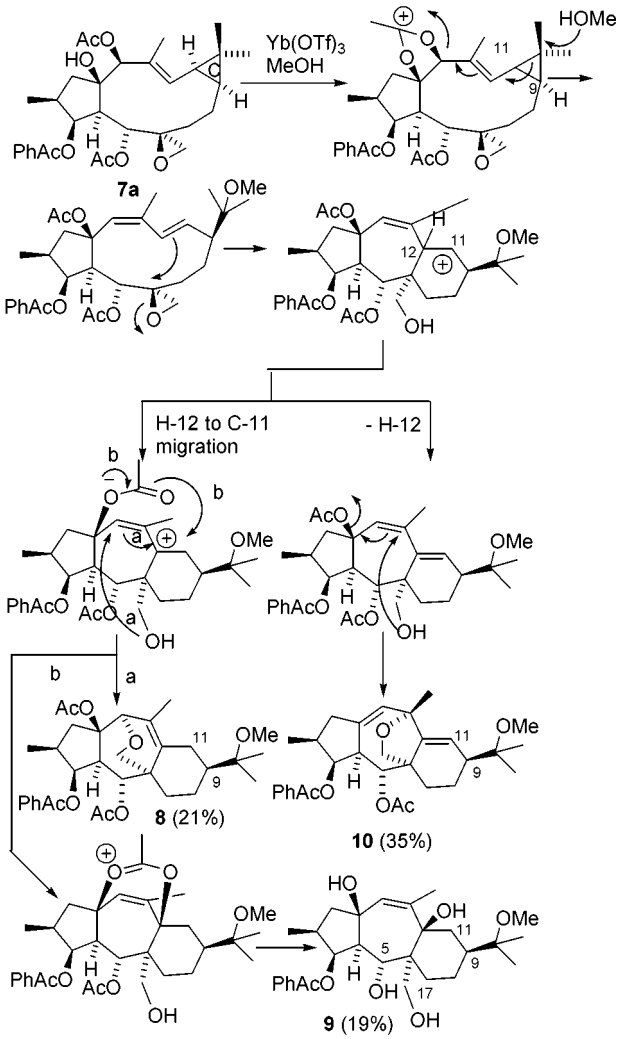
(10) Hohmann, J.; Evanics, F.; Dombi, G.; Molnár, J.; Szabó, P. *Tetrahedron* **2001**, *57*, 211−215.

(11) Ishiguro, T.; Kondo, Y.; Katemoto, T. *Tetrahedron* **1975**, *31*, 305−309.

Scheme 3



Scheme 4



fashion with C-15, the electrophilic tertiary carbon bearing the acetate, while a solvolytic process replaces the 5-acetyl with a formyl. After isopropylene to isopropylidene isomerization, **5** and **6** were eventually obtained.

To increase the nucleophilicity of the endocyclic double bond and exploit new avenues of reaction, reduction of the enone carbonyl of **1a** and **1b** was investigated under a variety of conditions. With most reducing agents, complex mixtures were obtained, but $NaBH_4$ in dioxane gave a clean reaction. Reduction of the 14-keto group occurred with attack from the α-face, affording, after acetyl migration, the tertiary alcohols **7a** from **1a** and the allylically rearranged ester **7b** from **1b**. Both compounds were obtained, as the only reaction products, in almost quantitative yield[12] and were highly prone to rearrangement. Among the systems tested to trigger the reaction, the mild Lewis acid $Yb(OTf)_3$[13] gave better yields compared to various protic acids and stronger Lewis acids ($BF_3{\cdot}Et_2O$, $SnCl_4$, Et_2AlCl). Thus, **7a** afforded a mixture of three abeomyrsinanes[14] (**8**−**10**, Scheme 4), while **7b** underwent a series of deep-rooted rearrangements, eventually affording the bridgehead polycyclic compounds **11** and **12** (Scheme 5).

Compounds **8**−**10** are the result of a process mediated by the formation of a C-*seco*-lathyradiene. This then undergoes transannular cyclization with *exo*-opening of the epoxide ring. After a series of hydride shifts, the positive charge is eventually quenched in an intramolecular way by oxygen trapping (Scheme 4).[15]

In the exomethylene alcohol **7b**, opening of the cyclopropane ring can be coupled to either ionization of the allylic 12-acetate and generation of a diene system or after transannular cyclization to the departure of the 15-hydroxyl. The latter generates **11**, having a bridgehead cagelike structure, while the diene system undergoes a transannular Diels−Alder reaction,[16] eventually affording the tetracycle **12** (Scheme 5).[17]

The chemistry involved in the acid-catalyzed rearrangement of the lathyranes **1a**,**b** and **7a**,**b** is remarkable and highlights the role of the γ-cyclopropyl enone moiety as a

(12) The success of this protocol might be related to the low solubility of the reaction products (**7a**, **7b**) in dioxane. In alcohols and ether, where a major solubility can be attained, complex mixtures were obtained, presumably because of degradation of the reduction products in the reaction medium. The reasons underlying the allylic rearrangement leading to **7b** are unclear and possibly related to transannular interaction between the exomethylene and the endocyclic double bond.

(13) Kobayashi, S. *Synlett* **1994**, 689−701.

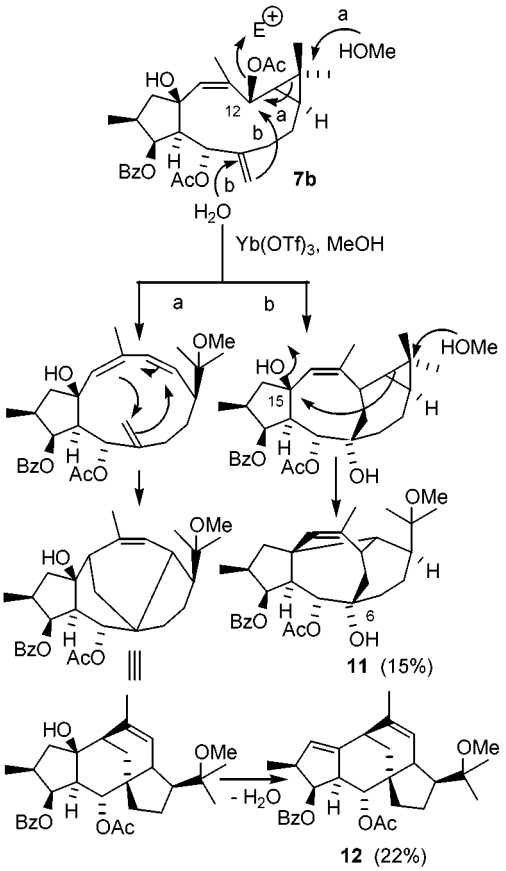
(14) The carbon skeleton of **8**−**10** differs from that of myrsinanes only for the location of the isopropyl side chain, which in the natural products is bound to C-11 (and not to C-9 as in **8**−**10**) as a result of a different regiochemistry of cyclopropane opening. (Appendino, G.; Belloro, E.; Tron, G. C.; Jakupovic, J.; Ballero, M. *J. Nat. Prod.* **1999**, *62*, 1399−1404).

(15) The loss of the 5-acetate in **9** is not surprising, since lanthanide Lewis acids are known to catalyze the cleavage of acetates when nearby coordinative groups are present, as in the 17-hydroxyl in the 5-acetyl derivative of **9** (Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. *Tetrahedron Lett*. **1999**, *40*, 1689−1692).

(16) Deslongchamps, P. *Pure Appl. Chem*. **1992**, *64*, 1831−1847. A cationic cyclization mechanism is also possible, though the involvement of a secondary cation is required.

(17) Lanthanide Lewis acids are known to promote Diels−Alder reactions (Kobayashi, S. *Eur. J. Org. Chem*. **1999**, 15−27).

Scheme 5



latent site of diversity. Even more surprising is, however, the observation that, despite the central role of lathyranes in the biogenesis of the *Euphorbia* diterpenoids, all compounds obtained in the cyclization reactions belong to skeletal types unknown within natural products. From a mechanistic standpoint, a common feature of the various reaction is the opening (or expansion) of the cyclopropane ring. This drives a host of further C−C and C−O bond reorganizations, generating an electron-rich enol or dien(ol) system that is eventually trapped by an electrophilic sink (6,17-epoxide, tertiary acetoxyl at C-15) or by a dienophile (6,17-double bond).

In conclusion, highly functionalized macrocyclic epoxyolefins and polyolefins such as the *Euphorbia* factors L_1 and L_3 are endowed with a remarkable potential to generate rigid polycyclic structures not easily accessed by other methods. The percentage yield of the transannular reactions was in some cases unimpressive. Nevertheless, the starting materials are easily available and the reaction mixtures simple to separate. A structurally diverse library of densely functionalized and stereochemically rich polycyclic compounds to screen against biological targets could thus be obtained.

The generation of molecules with different scaffolds is a major challenge for diversity-oriented synthesis,[1b] and we have shown how the incorporation of complementary reactive elements into a functionalized macrocycle core can indeed achieve this goal.

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Supporting Information Available: Experimental procedures and spectroscopic characterization (IR data; HRMS data; ^{1}H and ^{13}C NMR data) of all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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